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Subject Environmental Defense comments on 3-cyclohexene-1 -carboxylic acid, 3-cyclohexen-1 -ylmethyl ester (CAS# 261 l-00-9)

(Submitted via Internet 6/2/06 to hppt.ncic@epa.gov,jov, boswell.Karen@epa.gov, chem.rtk@epa.gov, MTC@mchsi.com, and Kdnitsch @ dow.com)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for **3-cyclohexene-1 -carboxylic acid, 3-cyclohexen-1 -ylmethyl ester (CAS# 2611-00-9).**

The Dow Chemical Company, in response to EPA's High Production Volume (HPV) Chemical Challenge, has submitted a test plan and robust summaries for 3-cyclohexene-1 **-carboxylic** acid, 3-cyclohexen-1 **-ylmethyl** ester (Diene 221) and supporting summaries for a related chemical, tetrahydrobenzaldehyde (THBA). THBA is proposed as a surrogate for Diene 221 because it is the monomer used in the synthesis of Diene 221.

According to the test plan, Diene 221 is synthesized in a closed system and used at the same location at which it is produced. The sponsor maintains that the unnamed finished product contains no more than "traces" of un-reacted Diene 221. However, no information is provided to confirm this claim or quantify what is meant by "traces" of Diene 221 present in the final product. Nevertheless, this submission proposes that, for HPV review, Diene 221 be considered a closed system intermediate and thus subject to less thorough data requirements than for chemicals that are more likely to be released into the environment. We defer to EPA as to whether the sponsor has sufficiently documented closed-system intermediate status with respect to manufacturing, but believe that quantitative data on residual amounts in final products must be provided to support this claim.

General Comments:

On review of this submission, we see that the robust summaries for both Diene 221 and THBA consist of IUCLID database files previously submitted as part of the European Risk Assessment Program on Existing Substances. As such, they contain numerous blank pages and dozens of headings without data. Whereas we are not opposed to the use of IUCLID reports to address the **SIDS** elements required under the HPV Challenge, we do think they should have been reformatted to fit HPV guidelines.

Many of the studies described are old, used too few animals and were not conducted under GLP. Some of the more recent studies of THBA were conducted under GLP and are acceptable; however, we do not believe the sponsor has made a sufficient case for reliance on THBA as a surrogate for Diene 221. Some of the more notable differences in properties of THBA and Diene 221, as illustrated by data contained in this submission, are significant differences in volatility, partition coefficient and water solubility. These properties could result in very different toxicities to aquatic organisms and/or mammals. This is best illustrated by water solubility data provided in Table 2 of the test plan (note that the units used in Table 2 differ for the two compounds). THBA has a measured water solubility of 5 g/L, whereas it has been calculated that only 1.94 mg of Diene 221 would be soluble in a liter of water. This marked difference in the water solubility of the two compounds, supported to some degree by the calculated partition coefficients, would be expected to result in marked differences in bioaccumulation in aquatic organisms as well as more systemic absorption by mammals. These differences could in turn account for marked differences in toxicity. Thus, studies of aquatic toxicity should be conducted.

The cursory studies of mammalian toxicity suggest Diene 221 has minimal acute toxicity to mammals. However, data on repeated dose toxicity and reproductive/developmental toxicity are not available for either Diene 221 or the proposed surrogate, THBA. Therefore, the sponsor should conduct a repeated dose toxicity study of Diene 221 using a protocol that is designed to include determinations of reproductive/developmental endpoints.

Specific Comments:

1. The robust summaries contain no references to data that are publicly available. Also, an individual named Kent Woodburn is referenced a number of times as a source of personal communications. His area(s) of expertise are never mentioned and he is not otherwise identified or mentioned in the list of references. These references should be properly cited or deleted.
2. All of the endpoint values provided for Diene 221, except for some rather poorly designed acute toxicity studies, are estimated. In some cases this is permissible, while in others, e.g., partition coefficient, water solubility, transport in the environment and all aquatic toxicity data, measured data need to be provided.
3. In section 1.3, the purity of the test compound is given as “typical for marketed substances”. Given the variable purity of marketed substances and the lack of data for Diene 221, more quantitative information needs to be provided.
4. Genetic toxicity studies are relatively quick, easy, economical and do not involve the use of live animals. We see no reason why they should not be conducted.

5. If THBA is to be proposed for use as a surrogate for Diene 221, the available data for both chemicals should be provided in a single set of robust summaries and supported by some discussion of those chemicals' similarities and differences that may be relevant to the respective SIDS element required by the HPV Challenge.
6. In Table 1 of the test plan, data for repeated dose toxicity and genetic toxicity are said to be available for Diene 221, yet they have not been described in this report. If acceptable studies of these endpoints are available, they need to be included.

Summary:

Whereas it appears likely that Diene 221 qualifies as a closed-system intermediate, and that it is probably metabolized to THBA and the respective acid, we do not believe the data available for either of these chemicals adequately address the SIDS elements required under the HPV Challenge. Further, we do not consider, based on the data provided, THBA to be an adequate surrogate for Diene 221 to address all SIDS elements.

Thank you for this opportunity to comment.

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